REMARKS

Claims 1-16 presently appear in this case. Claims 13-15 have been withdrawn from consideration. No claims have been allowed. The official action of November 26, 2002, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to glycosylated icIL-1ra-II, which does not exist in glycosylated form in nature. The invention further relates to an expression vector encoding a signal peptide of a protein that is normally expressed and secreted by human cells joined to a DNA segment encoding the icIL-1ra-II and operably linked to a promoter sequence. Isolated host cell lines transformed with such an expression vector, and methods for producing recombinant icIL-1ra-II by culturing such a host cell line are also claimed. The invention further relates to pharmaceutical compositions comprising such glycosylated protein and methods of use.

The examiner has acknowledged applicants' election with traverse, but states that the technical feature allegedly linking the inventions of Groups I-III does not constitute a special technical feature as defined by PCT Rule 13.2 as it does not define a contribution over the prior art.

Accordingly, the requirement has been deemed proper and made final.

This restriction requirement is again respectfully traversed. For the reasons that will be discussed in detail hereinbelow, the examiner's obviousness rejection has been overcome. Accordingly, the special technical feature does define a contribution over the prior art. Thus, if the examiner agrees to withdraw the obviousness rejection, then the non-elected groups should be rejoined and examined in this case.

It is noted that the examiner has acknowledged applicants' claim for priority to Israeli application 126562 under 35 U.S.C. §119(a)-(d).

The examiner has objected to the disclosure because of the presence of non-disclosure-related text at line 10 of page 24 and because the disclosure fails to refer to the foreign application in the first paragraph of the specification.

With respect to the first objection, page 24 has now been amended in order to eliminate the non-disclosure-related text. With respect to the second part of the objection, this objection is respectfully traversed.

The only rule that applicants are aware of requiring benefit information to appear in the first paragraph of the

specification is 37 C.F.R. §1.78(a)(2)(iii). However, if the examiner will review this rule, it will be seen that it applies only to reference to prior-filed, co-pending non-provisional applications or claiming benefit under 35 U.S.C. §120 of an earlier-filed international application designating the United States. There is no requirement to insert reference to a foreign priority application to which benefit is claimed under 35 U.S.C. §119(a)-(d). Furthermore, 37 C.F.R. §1.78(a)(2)(iii) states that if an Application Data Sheet is filed, the specification does not need to be amended even for U.S. benefit data. In this case, an Application Data Sheet is of record. Thus, for both reasons, there is no requirement to amend the first paragraph of the specification. If this objection is to be repeated, it is requested that the examiner cite authority for the requirement.

Claims 3-6, 9-12 and 16 have been rejected under 35 U.S.C. §101 because the claimed invention is directed to non-statutory subject matter. The examiner states that the host cell claims read on a transgenic human, which is non-statutory subject matter. The examiner recommends that "A host cell" be replaced by "An isolated host cell" to overcome this part of the rejection.

The host cell claims have now been amended to read on "An isolated host cell line". As a single cell is never

isolated, it is believed that the cell line language is more accurate and is at least implicit from the specification. This amendment obviates the examiner's rejection.

The examiner states that claims 9-12 and 16 recite a glycosylated icIL-1ra-II and, thus, read on a product of nature. The examiner recommends that the word "isolated" or "purified" be inserted to overcome this rejection. This part of the rejection is respectfully traversed.

Glycosylated icIL-1ra-II does not exist in nature. See page 5, line 20, of the present specification. In nature, the protein is intracellular only and, thus, is not glycosylated. Glycosylation is part of the secretion mechanism. Thus, as glycosylated icIL-1ra-II is not a product of nature, reconsideration and withdrawal of this rejection is respectfully urged.

Claims 1-12 and 16 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Pecceu and Bjorkdahl in view of Muzio. The examiner states that Pecceu teaches an expression vector comprising a DNA segment and encoding the signal peptide of human growth hormone and a DNA segment encoding the mature form of IL-1β. The examiner states that the expression of this fusion protein in CHO cells results in secretion of a glycosylated form of IL-1β that was recovered and shown to be biologically active. The examiner believes

that these results suggest that fusion of mature IL-1β to a heterologous signal peptide allows the protein to cross the membrane of the rough endoplasmic reticulum and to follow the pathway of a typical secretory protein. The examiner states that Bjorkdahl teaches a fusion protein wherein the signal sequence from an IL-1 receptor agonist was ligated to the cDNA encoding the mature form of IL-1β and that transfection of B16 melanoma cells with the expression vector resulted in the secretion of biologically active L-1β. The examiner concedes that neither Pecceu nor Bjorkdahl teach expression of a fusion protein comprising icIL-1ra-II. The examiner states that Muzio teaches intracellular expression of icIL-1ra-II in COS cells, as well as a method for producing the recombinant icIL-1ra-II, and a pharmaceutical composition containing it. The examiner considers it obvious to construct a fusion protein comprising a signal peptide of a protein which is normally expressed and secreted by human cells, such as the signal peptide of human growth hormone as taught by Pecceu and Bjorkdahl and the interleukin-1 receptor antagonist type II as taught by Muzio to express and to produce the secreted icIL-1ra-II in a host cell, including an isolated human cell, with reasonable expectation of success. The examiner considers it routine to produce a secretory protein by fusion of a non-secretory protein with a signal peptide of another secretory

protein, as exemplified by Bjorkdahl and in view of the successful use of the hGH signal protein in producing a secretory IL-1β by Pecceu and in view of the fact that icIL-1ra-II has important biological activity. This rejection is respectfully traversed.

As to the disclosure of Pecceu, the examiner's attention is invited to the present specification in the paragraph bridging pages 2 and 3, and in the first paragraph of page 5. These passages explain why no reading of Pecceu could have made it reasonably predictable whether or not the hGH signal peptide would drive the expression of icIL-1ra-II in a mammalian cell expression system. The icIL-1ra-II protein is naturally expressed only intracellularly and is not secreted from the cell. In Pecceu and Bjorkdahl, the hGH signal peptide, or another signal sequence, was used to express and secrete the mature form of IL-1β. However, the mature form of IL-1β is naturally secreted from the cells in which it is produced, although indirectly. A precursor protein is first produced which, after intracellular processing, is secreted from the cell. Thus, it would be expected that the secreted form of IL-1β would be biologically active after it is secreted as the mature form of IL-1β is naturally secreted.

On the other hand, icIL-1ra-II is strictly an intracellular protein. It is never secreted in the natural environment. It could not have been reasonably predictable that this protein would still be active after being glycosylated and secreted. IL-1β is a secreted protein. Even though its mechanism of secretion is different from most proteins, it is still a secreted protein and is biologically active outside of the cell. Thus, it would not be obvious to substitute the hGH signal sequence or any other signal sequence for the V3 of Muzio, nor would it have been obvious that the result of that fusion with cDNA would be expressed and would maintain its biological activity.

Furthermore, Pecceu discloses, for example in the conclusion section at page 257:

> When the biologically active part of IL-1β was preceded only by a methionine and synthesized in CHO cells, a considerable percentage of the IL-1β produced was quite unexpectedly found in the culture medium. ... This suggests that certain molecules seem to be exported from the cell - either actively or passively - directly from the cytoplasm.

Thus, since the CHO system of Pecceu that is used allows IL-1β to be secreted regardless of whether or not the hGH signal protein is present, it is not clear that it is the hGH signal peptide that causes the secretion of the IL-1β in Pecceu. Thus, it could not be predicted with a reasonable degree of

certainty that a protein, such as icIL-1ra-II, which is only expressed intracellularly and is not naturally secreted from the cell, could be made to be secreted in large quantities in a recombinant mammalian expression system when fused to an hGH signal peptide or to a signal peptide of another secretory protein. Furthermore, Pecceu reports no results as to whether the non-natural glycosylated form of IL-1β creates an immunological reaction when administered to a human or is recognized as a cell protein. Bjorkdahl and Muzio supply none of these deficiencies of Pecceu. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

The examiner's attention is also invited to the International Preliminary Examination Report, which is of record in this case. This report finds that at least claims 2, 6, 8 and 15 are novel and unobvious. The international examiner did not consider the use of the specific hGH signal protein as being obvious as no indications in Pecceu are given to combine the teachings of Muzio and Pecceu, and as Muzio does not mention the possible fusion of icIL-1ra-II with another protein, and Pecceu does not mention the use of the hGH signal peptide in fusion with other proteins than IL-1β. Furthermore, the international examiner noted the effect of the fusion of the proteins of Pecceu as being somewhat unclear as the authors also describe elevated levels of secreted IL-1β

upon the mere addition of a methionine at the N-terminus of the protein. Consequently, the international examiner considered the creation of such a fusion protein to comprise an inventive step and, thus, claim 2 was considered to comply with the regulations concerning inventivity. While it is believed that claim 1 is also allowable for the reasons as discussed hereinabove, certainly claim 2 should be indicated to be allowable for the same reasons that it was found allowable by the international examiner.

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §101 and 112. Reconsideration and allowance are, therefore, earnestly solicited.

Respectfully submitted,

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